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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,908	01/08/2009	**Xiangbin Wang**	11774-006-999	3643

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,908	WANG ET AL.	
	Examiner	Art Unit	
	MARK HALVORSON	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *21-24,27 and 31-40* is/are pending in the application.

5a) Of the above claim(s) *34-40* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *21-24, 27 and 31-33* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 21-24, 27 and 31-40 are pending.

Claims 34-40 have been withdrawn.

Claims 21-24, 27 and 31-33 are currently under examination.

Objections to Specification withdrawn

The objections to the specification are withdrawn in view of Applicant's amendment to the Specification.

35 USC § 102(b) rejections withdrawn

The rejections of claims 21-24, 26, 28-31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510) are withdrawn in view of Applicants' amendments to claim 21.

The rejections of claims 21-24, 31 and 33 under 35 U.S.C. 102(b) as being anticipated by WO 02/83738, (published 10 April 2002) as evidenced by the national stage application US Patent Application Publication 2005/0175606, published 11 August 2005) are withdrawn in view of Applicants' amendments to claim 21.

35 USC § 112 1st paragraph rejection maintained

The rejections of claims 21-24, 27, 31and 33 are rejected under 35 U.S.C. 112, first paragraph are maintained.

Applicants argue that the instant amendments place the claims within a scope well enabled and supported by the Specification as filed and meet the requirements of 35 USC 112, first paragraph.

However, claim 21 still recites the limitations "single chain antibody fragment of a variable region" which is interpreted as being an antibody fragment that does not comprise both the V_H and V_L antibody regions. Given the disclosure of the specification and the teaching in the art that indicates the unpredictability of treating cancer and

autoimmune disease, one skilled in the art could not predictably make a functional tri-specific antibody comprising an anti-tumor associated antigen antibody fragment that does not comprise the complete antigen-binding fragment, an anti-CD3 antibody fragment that does not comprise the complete antigen binding fragment and an anti-CD28 antibody fragment that does not comprise the complete antigen binding fragment. Therefore, in view of the breadth of the claims, lack of guidance in the specification, the absence of working examples, and the state of the art, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

35 USC § 103(a) rejections maintained

The rejection of claims 21-24, 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916).

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment, wherein the anti-tumor associated antigen is CEA.

Song et al discloses a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment. (paragraph 1.2) Song et al's single chain tri-specific antibody comprises a C myc tag (paragraph 1.3) and two interlinkers, an interlinker-Fc and an interlinker-HSA. (paragraph 2.1).

Song et al does not disclose a single chain tri-specific antibody comprising in tandem an anti-CEA antibody fragment, a first interlinker, an anti-CD3 antibody fragment a second interlinker and an anti-CD28 antibody fragment.

Holliger et al disclose two bispecific antibodies, an anti CEA X anti-CD3 antibody and an anti-CEA X B7 fusion protein. (page 2910, 1st column).

One of ordinary skill in the art would have been motivated to apply Holliger et al's anti-CEA antigen binding antibody fragment to Song et al's single chain tri-specific

antibody because Song et al disclose that the single chain tri-specific antibody could be a powerful CD3-based immunotherapy without simultaneous administration of other costimulatory molecules (page 3, 1st paragraph). Furthermore, Holliger et al disclose that CEA is a model antigen as one of the most well-characterized tumor antigens on solid tumors. (page 2915, 1st column). It would have been prima facie obvious to substitute Song et al's single chain tri-specific antibody comprising an anti-ovarian carcinoma scFv with Holliger et al's anti-CEA antigen binding antibody fragment to make a single chain tri-specific antibody comprising an anti-CEA scFv.

The rejections of claims 21-24, 27 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Song e al (Acta Biochimica Biophysica Sinica, 2003, 35:503-510, cited previously) in view of Holliger et al (Cancer Res, 1999, 59:2909-2916, cited previously) in further view of Koga et al (Hybridoma, 1990, 9:43-56) and Robinson et al. (US Patent No. 5,618,920, issued April 8, 1997) are maintained.

The claims are drawn to a single chain tri-specific antibody comprising in tandem an anti-tumor associated antigen antibody fragment, a first interlinker, an anti-CD3 antibody fragment, a second interlinker and an anti-CD28 antibody fragment, wherein the anti-tumor associated antigen is CEA.

Song et al has been described supra.

Holliger et al has been described supra.

Neither Song et al nor Holliger et al disclose an anti-CEA antigen binding fragment comprising SEQ ID NO:1.

Koga et al disclose the anti-CEA monoclonal antibody (page 44) that was used to make the anti-CEA scFv. (page 17 of the specification)

Robinson et al teach the determination of nucleic acids encoding VH and VL of any known antibody and use of said VH and VL to produce FV (see column 1-45, and columns 12-22). Robinson et al teach that "The invention also produces consensus sequences and specific oligonucleotide sequences useful as probes for hybridization and priming cDNA synthesis of any hybridoma mRNA coding for variable regions of any

desired specificity." (see column 4, last paragraph). The nucleic acid constructs of the VH and VL are used to make reconstructed antibodies, such as chimeric antibodies, that prevent harmful hypersensitive reactions in humans (column 1, lines 41-43).

One of ordinary skill in the art would have been motivated to apply Robinson et al's method determination of nucleic acids encoding VH and VL of an antibody to Koga et al's anti-CEA antibody because Robinson et al states teach the determination of nucleic acids encoding VH and VL of any known antibody while Koga et al disclose that the antigen recognized by PAM-1 is present on gastric adencarcinomas. One of ordinary skill in the art would have been motivated to apply Robinson et al and Koga et al's anti-CEA antibody's VH and VL to Song et al and Holliger et al's single chain tri-specific antibody comprising an anti-CES scFv because Koga et al disclose that the anti-CEA antibody localized to tumor tissue *in vivo*. (page 51, 2nd paragraph). It would have been prima facie obvious to have substituted Song et al and Holliger et al's anti-CEA scFv with Robinson et al and Koga et al's anti-CEA antibody's VH and VL to make a functional single chain tri-specific antibody comprising an anti-CEA scFv.

Applicants argue that *Song et al.* and *Holliger et al.,* individually or in combination, do not disclose a linear single chain recombinant tri-specific antibody scTsAb comprising in tandem an anti-Carcinoma-Embryonic Antigen single chain antibody fragment of a variable region (scFv) of the tri-specific antibody, an Fc linking peptide, an anti-CD3 single chain antibody fragment of the variable region (scFv), a human serum albumin linking peptide, and an anti-CD28 single-domain antibody fragment. Applicants argue that the vectors pTRI and psTRI disclosed in *Song et al.* encode for a trispecific antibody carrying Fc hinges at both ends, which *in vivo* form intra- and intermolecular disulfide bonds. Applicants argue that the trispecific antibodies disclosed in *Song et al.* either form circular antibodies by intramolecular disulfide bonds and are thus not linear or form polymeric antibodies by intermolecular disulfide bonds that are not single-chain antibodies.

Applicants arguments have been considered but are not persuasive. Song et al does not disclose fragments of Fc hinges at both ends of the constructs of vectors pTRI

and psTRI to form a circular fragment as disclosed in WO 02/83738. Song et al does not disclose the use of fragments of Fc hinges nor that the encoded trispecific antibody would circularize after expression. Furthermore, even if the trispecific antibody of Song et al did have fragments of Fc hinges at both ends of the construct, the expressed trispecific antibody would be linear until conditions were suitable for cyclization via intermolecular dilsulfide bonds to occur. In addition, Holliger et al disclose antibody constructs that do not comprise the Fc hinge fragments and would not form a circular fragment as disclosed in WO 02/83738 under suitable conditions such as when used *in vivo*.

NEW REJECTIONS: Based on the Amendment

Claim Objections

The amended claims are object to because the withdrawn claims must be written out. MPEP 714 states that "Each amendment document that includes a change to an existing claim, cancellation of an existing claim or addition of a new claim, must include a complete listing of all claims ever presented, including the text of all pending and withdrawn claims, in the application".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-24, 27 and 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 has the limitation "single chain antibody fragment of a variable region" followed in parentheses by (scFv). However, the abbreviation scFv stands for single-

chain variable fragment. The term "single-chain variable fragment" is well known in the art and it is known to encompasses both the V_H and V_L regions. The term used in the present claims "single chain antibody fragment of a variable region" is not well known in the art and can be interpreted to be a fragment of an antibody that does not encompass both the V_H and V_L regions. Amended the claim to clearly indicate that scFv stands for a "single-chain variable fragment" would obviate this rejection.

Summary

Claims 21-24, 27 and 31-33 stand rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Misook Yu, can be reached at (571) 272-0839. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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